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JC948 U.S. PTO 10/13/00

UTILITY PATENT APPLICATION TRANSMITTAL

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ADDRESS TO:

Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Attorney Docket No. 99,829-A

First Named Inventor T.G. Dinan

Express Mail No. EL442910811US

Total Pages

APPLICATION ELEMENTS	ACCOMPANYING APPLICATION PARTS
1. ☒ Transmittal Form with Fee	8. ☐ Assignment Papers
2. ☒ Specification (including claims and abstract) [Total Pages 11]	9. ☐ Power of Attorney
3. ☐ Drawings [Total Sheets 0]	10. ☐ English Translation Document (if applicable)
4. ☐ Oath or Declaration [Total Pages]	11. ☐ Information Disclosure Statement (IDS)
a. ☐ Newly executed	☐ PTO-1449 Form
b. ☐ Copy from prior application **[Note Boxes 5 and 17 below]**	☐ Copies of IDS Citations
i. ☐ Deletion of Inventor(s) Signed statement attached deleting inventor(s) named in the prior application	12. ☐ Preliminary Amendment
5. ☐ Incorporation by Reference: The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	13. ☒ Return Receipt Postcard (Should be specifically itemized)
6. ☐ Microfiche Computer Program	14. ☐ Small Entity Statement(s)
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c. ☐ Statement verifying above copies	16. ☐ Other:

17. ☒ This is a CONTINUING APPLICATION. Please note the following:

a. ☒ This is application claims the priority of Provisional Application 60/161,117 filed October 22, 1999.

b. ☐ Cancel in this application original claims ____of the prior application before calculating the filing fee.

c. ☐ Amend the specification by inserting before the first line the sentence: This is a ☐ continuation ☐ divisional ☐ continuation-in-part of application Serial No.

d. ☐ The prior application is assigned of record to

UTILITY PATENT APPLICATION TRANSMITTAL			Attorney Docket No. 99,829-A	
APPLICATION FEES				
BASIC FEE				$ 710.00
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total Claims	6 -20=		x $18.00	$
Independent Claims	1 - 3=		x $78.00	$
☐ Multiple Dependent Claims(s) if applicable			+$270.00	$
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18. ☐ Please charge my Deposit Account No. 13-2490 in the amount of $

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22. CERTIFICATE OF MAILING

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Name Reg. No.	John J. McDonnell 26,949
Signature	
Date	October 13, 2000

U.S. EXPRESS MAIL NO.: EL442910811US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(MBHB Case No. 99,829-A)

TITLE : Treatment and prevention of gastrointestinal disease using antagonists or partial agonists of 5HT1a receptors

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This application claims the priority of Provisional Application 60/161,117 filed October 22, 1999.

FIELD OF THE INVENTION

The present invention provides a method for preventing and treating gastrointestinal diseases such as dyspepsia, irritable bowel disease and chemotherapy-associated nausea by administering an antagonist or partial agonist of 5HT1a receptors.

BACKGROUND OF THE INVENTION

Dyspepsia is a common symptom ranging in prevalence from 26% in the United States to 41% in England (1). Whilst only 1 in 4 patients seek medical help (2) the condition results in significant health care costs (3) and an organic cause is found in only 40% of patients. The Rome criteria for diagnosing idiopathic or nonulcer dyspepsia (NUD) were put forward in 1991 and consist of chronic or recurrent upper abdominal pain or discomfort in the absence of obvious pathology (4). The Rome group suggested subcategorising NUD into ulcer-like, reflux-like, dysmotility-like and non-specific dyspepsia. This classification has been questioned on the grounds that there is a marked overlap of symptoms and an overlap between the symptoms and those of the irritable bowel syndrome (5).

Conventional diagnostic evaluation (endoscopy, ultrasonography, 24h ambulatory pH monitoring) does not reveal a structural or biochemical abnormality to explain NUD. Attempts at elucidating the pathophysiology of the condition have produced inconsistent findings (6) and a wide array of theories are currently put forward (7).

Serotonin (5HT) is a neurotransmitter both in the enteric nervous system (8) and in the brain (9). It plays a key role in regulating gut physiology, including peristalsis and intestinal tone (10). Animal studies have shown that intracerebroventricular injection of fenfluramine (a serotonin releasing agent) inhibits gastric emptying (11). Selective serotonin reuptake inhibitors, such as fluoxetine and sertraline, are widely used in the treatment of depression and produce a transient syndrome similar to NUD in up to 30% of patients treated (12).

Studies indicate that a central 5HT1a receptor hypersensitivity may be involved in the pathophysiology of NUD (13,14). The release of prolactin from the anterior pituitary is under dopamine inhibition and under 5HT stimulation, probably at the level of the hypothalamus (15). Buspirone is an azaspirodecanedione, which acts as a partial agonist at the 5HT1a receptor (16) and stimulates prolactin release. We have established that prolactin release following buspirone challenge is enhanced in NUD indicating 5HT1a receptor supersensitivity in this condition.

We have demonstrated this in a clinical study that extends our previous findings reported in U.S. Patent No. 5,403,848.

A total of 109 subjects, 50 NUD patients (39 female/11 male) and 59 healthy comparison subjects (32 female/28 male) gave fully informed consent to take part in the study, which had Ethics Committee approval. The mean±SD age of the patients was 35.6±12.2 years (Range 20-62) and of the comparison group 27.2±7.6 years (Range 20-52). At 0830h subjects had a cannula inserted in a forearm vein. Buspirone (30mg) or matching placebo was administered orally at 0900h (Time 0). Blood was taken at 0, 30, 60, 90, 120 and 180min. Prolactin levels rose in all subjects challenged with buspirone. The mean±SD AUC in patients was 46±35 and in healthy subjects 24±35. A 2-way repeated measures ANOVA yields a significant group X time interaction, with differences significant at 60min ($p<0.05$), 90 min ($p<0.01$) and 120 min ($p<0.05$). Prolactin concentration at 90 min provided the best discrimination between the two groups.

According to the present invention, what is required to treat non-ulcerative dyspepsia is the administration of effective amounts of a substance that reduces the sensitivity of 5HT1a receptors and we have discovered that pindolol, which has affinity for 5HT1a receptors has beneficial effects in subjects suffering from non-ulcerative dyspepsia.

SUMMARY OF THE INVENTION

The present invention provides a means for prevention and treatment of gastrointestinal disease by administration of a substance that reduces the sensitivity of 5HT1a receptors. A preferred means is the administration of RS pindolol or a salt thereof. An especially preferred means is the administration of S (-) pindolol or a salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

As noted earlier, this invention can use any substance that is an antagonist or a partial agonist of 5HT1a receptors such that the sensitivity of 5HT1a receptors described above is reduced.

Pindolol is a beta adrenergic antagonist, used in the treatment of hypertension and angina. It also has affinity for 5HT1a receptors of a similar magnitude as its affinity for beta adrenergic receptors. Until now, no therapeutic applications of this phenomenon have been discovered. Pindolol is used therapeutically in hypertension and angina as the racemic substance, RS pindolol. Most or all of the pharmacological effects of pindolol are possessed by the isomer S (-) pindolol. The present invention utilizes pindolol to reduce the sensitivity of 5HT1a receptors and as a result to provide the means for prevention and treatment certain gastrointestinal diseases, including non-ulcerative dyspepsia. A preferred embodiment of the invention is the isomer S (-) pindolol or salts thereof. Another method utilizes the administration of cyproheptadine, described in U.S. Patents 5,324,738 and 5,403,848. The latter also describes a method for diagnosis of non-ulcerative dyspepsia by measuring the

responsiveness of 5HT1a receptors. RS pindolol has an advantage over cyproheptadine of greater selectivity for the 5HT1a receptor and S (-) pindolol has further advantages of greater potency and specificity.

The invention is likely to be effective in various presentations of gastrointestinal disease in which there is altered sensitivity of 5HT1a receptors. We have specific demonstration of the role of 5HT1a receptors in non-ulcerative dyspepsia, but there is likely to be also benefit in certain cases of irritable bowel syndrome, especially that occurring in the upper intestinal region and in certain cases of motility disorders (including nausea) caused by cancer chemotherapy.

Various pharmaceutical presentations are possible, including (but not limited to) tablets, capsules, oral solutions and suspensions and parenteral solutions. Included are also pharmaceutical formulations for oral use in which the active substance is released in a controlled and slower fashion such that the treatment may be administered less frequently.

The usual doses of RS pindolol and S (-) pindolol will be in the range of 2.5mg to 50mg daily in single or divided doses, depending upon the therapeutic response and the pharmaceutical form. The usual doses of S (-) pindolol will be lesser than those of RS pindolol since the former will be more potent because it is responsible for most or all of the pharmacological effects.

The invention is intended for the treatment of mammals, including humans.

The ability of the invention to treat gastrointestinal disease has been demonstrated in a clinical study.

EXAMPLE

Eleven patients suffering from non-ulcerative dyspepsia were recruited to a clinical study and gave informed consent. All were treated with pindolol 2.5mg three times daily. Seven of the 11 patients showed a significant improvement in symptoms within 1 week of commencing treatment. A further patient improved in the second week. Their responses were quantified using a standard rating scale (GSRS scores). The results demonstrated a substantial improvement with a reduction in average symptom severity of approximately 68% in three weeks, with the greatest improvement observed within one week.

Table 1. Mean symptom score (average of 11 patients)

Week	Mean GSRS Score
0	9
1	4.2
2	3.5
3	2.9

REFERENCES TO PREVIOUS PATENTS

T.G. Dinan and P.W.N. Keeling	U.S. Patent No. 5,324,783
T.G. Dinan and P.W.N. Keeling	U.S. Patent No. 5,403,848

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What is claimed is:

1. A method for preventing and treating gastrointestinal disease by means of administration of an effective amount of an antagonist or partial agonist of 5HT1a receptors.

2. A method according to claim 1 employing an effective amount of the racemic substance RS pindolol or a salt thereof.

3. A method according to claim 1 employing an effective amount of one of the enantiomers, S (-) pindolol of claim 2 or a salt thereof.

4. A method according to claim 1 in which effective amounts of RS-pindolol or S(-) pindolol or their salts are administered in a pharmaceutical dosage form that permits rapid release of the active substances.

5. A method according to claim 1 in which effective amounts of RS pindolol or S(-) pindolol or their salts are administered in a pharmaceutical dosage form that releases the active substances in a slow or controlled fashion that in turn permits administration of the active substances at lesser frequency than in claim 4.

6. A method according to claim 1 in which the gastrointestinal diseases are characterised as non-ulcerative dyspepsia or irritable bowel syndrome or chemotherapy-associated disorders of motility, including nausea.

ABSTRACT OF THE DISCLOSURE

The present invention provides a method for preventing and treating gastrointestinal diseases such as dyspepsia, irritable bowel disease and chemotherapy-associated nausea by administering an antagonist or partial agonist of 5HT1a receptors.